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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,126	02/27/2006	Mark Jozef Albert Waer	50304/113001	3050

21559 7590 01/24/2007

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EXAMINER	
YOUNG, SHAWQUIA	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,126	WAER ET AL.	
	Examiner	Art Unit	
	Shawquia Young	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13,14,16,17 and 19* is/are allowed.

6)☒ Claim(s) *15,18 and 20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 13-27 are currently pending in the instant application. Applicants cancelled claims 1-12 in a preliminary amendment.

I. Priority

The instant application is a 371 of PCT/BE04/00123, filed on August 27, 2004, which claims benefit of GB 0408955.3, filed on April 22,2004, which is also a CON of 10/651,604, filed on August 29, 2003.

II. Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

(1) Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and unclear. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a

question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 18 recites the broad recitation "alkylating agents" and "antimetabolites", and the claim also recites "alkyl sulfonates, aziridines, ethylenimines, methylmelamines, nitrogen mustards, and nitrosureas" and "folic acid analogs, purine analogs, and pyrimidine analogs" which is the narrower statement of the range/limitation, respectively.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(2) Claims 15, 18, 22 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising at least one pteridine derivative as found in claim 13 and additionally with one or more biologically active drugs selected from the group consisting of immuno-suppressant and/or immunomodulator drugs and antineoplastic drugs does not reasonably provide enablement for a pharmaceutical composition comprising at least one pteridine derivative as found in claim 13 and additionally with one or more

biologically active drugs selected from the group consisting of antihistamines and anti-allergic drugs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case

The nature of the invention

The nature of the invention is a pharmaceutical composition comprising at least one pteridine derivative according to claim 13, and further comprising one or more biologically active drugs selected from the group consisting of immuno-suppressant and/or immunomodulator drugs, antihistamines, antineoplastic drugs and anti-allergic drugs.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to pharmaceutical compositions comprising multiple active agents, one would need to consider drug-drug interactions.

For the preparation of pharmaceutical compositions containing multiple active ingredients, one needs to take into account drug-drug interactions. There are many types of antihistamines and anti-allergic drugs. For example, there are various types of antihistamines including first generation, second generation, and third generation H_1-receptor antagonists. First generation antihistamines (H_1-receptor antagonists) also can be used as anticholinergic agents, which increases the risk of adverse drug reactions. Other agents that possess antihistaminergic activity include tricyclic antidepressants,

antipsychotics, etc.

(<URL:http://en.wikipedia.org/wiki/Antihistamine>)

As found in Drugs of Today 39(5), 2003, 301-38, Obach discloses that in regards to any given pharmacokinetic drug-drug interaction, the two drugs involved can be considered as either the "perpetrator" drug or the "victim" drug. The perpetrator is the drug that affects the activity of an enzyme of protein involved in the metabolism or disposition of the victim drug. The victim drug is the one that either causes side-effects or toxicity due to increased exposure, or lack of efficacy due to exposure decreased to below that required for therapeutic effect (page 302). There are varying mechanisms of drug interactions such as the reduction in the rate of the metabolism of one drug by another, the irreversible inactivation of drug-metabolizing enzymes and the exposure to the victim drug is decreased (pages 303-304). Obach also discloses that there are a number of in vitro and in vivo experimental approaches to be taken to determine drug-drug interactions (page 304).

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present for the pharmaceutical compositions containing additional biologically active agents such as antihistamines and anti-allergic drugs is found on page 30. Page 30, while providing the listing of some broad biologically active agents such as antihistamines and anti-allergic drugs fails to provide any direction or guidance as to the breadth of these therapeutic agents. Furthermore,

for example, the specification does not disclose one single example of an antihistamine or anti-allergic drug in combination with applicants' pteridine derivative, nor does the specification disclose what the breadth of the terms "antihistamines and anti-allergic drugs" encompasses. Furthermore, there is no pharmaceutical composition actually prepared in the instant specification which contains any antihistamines or anti-allergic.

The breadth of the claims

The breadth of the claims is a pharmaceutical composition comprising at least one pteridine derivative according to claim 13, and further comprising one or more biologically active drugs selected from the group consisting of immuno-suppressant and/or immunomodulator drugs, antihistamines, antineoplastic drugs and anti-allergic drugs.

The quantity of experimentation needed and the level of the skill in the art

While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what antihistamines and anti-allergic drugs could be administered with applicants' instant pteridine derivatives without any direction found in the specification, and the drug-drug interactions of these agents with the pteridine derivatives in claim 13. While the level of skill in the art is high, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compositions exhibit the desired pharmacological activity. Thus, the specification fails to provide sufficient support of pharmaceutical compositions comprising at least one

pteridine derivative and and further comprising one or more antihistamine and/or anti-allergic drugs.. As a result necessitating one of skill to perform an exhaustive search for which biologically active agents can be combined with the compound of the formula I without negative drug-drug interactions.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which biologically active agents, for example which antihistamine and anti-allergic drug could be combined in a pharmaceutical composition with at least one pteridine derivative according to claim 13, with no assurance of success.

This rejection can be overcome, for example, by deleting the above claims.

(3) Claims 20-27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

Applicants are claiming a method of preventing or treating a pathologic condition selected from the group consisting of immune and auto-immune disorders, cardiovascular disorders, disorders of the central nervous system, cell proliferative disorders and allergic conditions by administering an effective amount of a pharmaceutical composition comprising as an active principle at least one pteridine derivative according to claim 13. See, for example, instant claim 20. Further, Applicants fail to identify all diseases or disorders that can be treated by using a pharmaceutical composition comprising a pteridine derivative according to claim 13. From the reading of the specification, it appears that Applicants are asserting that the embraced compounds, because of their mode of action would be useful in preventing or

treating any pathologic condition selected from the group consisting of immune and auto-immune disorders, cardiovascular disorders, disorders of the central nervous system, cell proliferative disorders and allergic conditions..

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the treatment of disorders of the central nervous system, for example, remains highly unpredictable. The various types of illnesses and disorders of the central nervous system have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. According to Magnus et al., diseases that affect the central nervous system include Alzheimer's disease, Parkinson's disease, and multiple sclerosis. It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease. (<URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>.)

In addition, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic

agents (*See* e.g., the Cecil Textbood of Medicine, 20th edition (1996), Vol. 2, page 1994). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Applicants are also claiming methods which include the prevention or treatment of various diseases such as cardiovascular disorders, auto-immune disorders (which includes lupus erythematosus and Sjögren syndrome) and cell proliferative disorders.

In regards to the prevention or treatment of various cardiovascular disorders, "Cardiovascular disorders" embrace a vast array of problems, many of which are contradictory to others. Thus, it covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris', the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis, elevated blood levels of triglycerides , of total cholesterol or of LDL cholesterol, arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound, let alone a genus of compounds, could possibly be effective against such disorders generally.

Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions.

Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, this trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

In regards to prevention and treatment of various autoimmune disorders, the causes of autoimmune disorders are still obscure. Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body. Today there are more than 40 human diseases classified as either definite or probable autoimmune diseases. Autoimmune diseases affect 5% to 7% of the population and almost all autoimmune diseases appear without warning or apparent cause. Autoimmune diseases include lupus erythematosus, psoriasis, Sjörgen syndrome, Crohn's disease, etc.
(<URL:http://en.wikipedia.org/wiki/List_of_amutoimmune_diseases>)

Sjörgen's syndrome is an autoimmune disorder in which immune cells attack and destroy the exocrine glands that produce tears and saliva. The hallmark symptoms of the disorder are dry mouth and dray eyes. In addition, the disorder may cause skin, nose and vaginal dryness, and may affect other organs of the body, including the kidneys, blood vessels, lungs, liver, pancreas, and brain. Sjörgen's syndrome is estimated to strike as many as 4 million people in the United States alone making it the

second most common autoimmune rheumatic disease. Diagnosing Sjörgen's syndrome is complicated by the range of symptoms a patient may manifest, and the similarity between symptoms from Sjörgen's syndrome and those caused by other conditions. There is neither a known cure for Sjörgen's syndrome nor a specific treatment to permanently restore gland secretion.
(<URL:http://en.wikipedia.org/wiki/ Sjörgen's_syndrome >)

Lupus erythematosus is a chronic autoimmune disease that is potentially debilitating and sometimes fatal as the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage. It can affect any part of the body, but most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system. The course of this disease is unpredictable, with periods of illness (called flares) alternating with remission. Lupus erythematosus is one of the several diseases known as the great imitator because its symptoms vary so widely it often mimics or is mistaken for other illnesses, and because the symptoms come and go unpredictably. Lupus research has dramatically increased in recent years but the exact cause of the disease is unknown and there is still no consensus on whether it is a single condition or a group of related diseases. As of 2006, there is no known cure for lupus erythematosus and treatment is restricted to dealing with the symptoms.
(<URL:http://en.wikipedia.org/wiki/ Lupus_erythematosus >)

The amount of direction or guidance present and the presence or absence of working examples

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the numerous diseases or disorders claimed herein. That a single class of compounds can be used to prevent or treat all pathologic condtions selected from immune and autoimmune disorders, cardiovascular disorders, disorders of the central nervous system, cell proliferative disorders and allergic conditions. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating or preventing any or all conditions by administering the instant claimed compounds.

The breadth of the claims

The breadth of the claims is a method of preventing or treating a pathologic condition selected from the group consisting of immune and auto-immune disorders, cardiovascular disorders, disorders of the central nervous system, cell proliferative disorders and allergic conditions by administering an effective amount of a pharmaceutical composition comprising as an active principle at least one pteridine derivative according to claim 13, generically embraced in the claim language.

The quantity of experimentation needed

The nature of the pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities for each of the diseases and disorders instantly claimed. The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to testing all diseases and disorders generically

embraced in the claim language, and when faced with the unpredictability of the pharmaceutical art. Thus, factors such as "sufficient working examples", "the level of skill in the art" and predictability, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

The level of the skill in the art

Even though the level of skill in the pharmaceutical art is very high, based on the unpredictable nature of the invention and state of the prior art and lack of guidance and direction, one skilled in the art could not use the claimed invention without undue experimentation.

This rejection can be overcome, for example, by deleting the method claims.

III. Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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